REMARKS

Introductory Matters

Claims 1-27 are pending in this application. Claims 1-27 stand rejected. Applicants have canceled claims 12, 13, 15, 18, 19, 21, and 26.

Applicants have amended claim 14 to recite specific cancers associated with Aurora-2 expression. Support for this amendment can be found throughout the specification and at page 2, line 24 through page 3, line 2.

Applicants have amended claim 16, which depends from claim 14, to recite "chemotherapeutic agent or anti-proliferative agent." Support for this amendment can be found throughout the specification and at page 30, lines 13-24.

Applicants have amended claim 20 to recite specific cancers associated with GSK-3 expression. Support for this amendment can be found throughout the specification and at page 18, lines 4-12. Applicants have also corrected a typographical error by deleting the repeated term "the method" in claim 20.

Applicants have amended claim 22 to depend from claim 20 (in light of cancelled claim 21) and to remove the term "GSK-mediated."

Applicants have amended claim 27 to recite specific diseases associated with Src expression. Support for this amendment can be found throughout the specification and at page 22, lines 12-32.

These amendments add no new matter.

THE OFFICE ACTION

35 U.S.C. § 112, first paragraph

Claims 11-27 stand rejected under 35 U.S.C. § 112, first paragraph as lacking enablement. The Examiner contends that the specification "while being enabling for the treatment of colon cancer, does not reasonably provide enablement for the treatment of all other diseases embraced by the instant claims." (August 30, 2005 Office Action page 2). Applicants traverse.

First, applicants respectfully point out to the Examiner that claims 11 and 23-25 do not relate to the treatment of any recited diseases. Because these claims do not relate to the treatment of any recited disease, Applicants respectfully request that the Examiner withdraw his rejection of claims 12, 11, 23-25 under 35 U.S.C. § 112, first paragraph.

In order to expedite prosecution, Applicants have canceled claims 12, 13, 15, 18, 19, 21, and 26. Applicants also have amended claims 14, 16, 20, 22, and 27 as described below. Accordingly, claims 14, 16, 17, 20, 22, and 27 are subject to the arguments set forth below.

The Examiner contends that the instant claims, which are "drawn to 'a method for inhibiting Aurora-2 kinase, GSK-3; Src; etc. activity' and 'a method of treating diseases mediated by Aurora-2, GSK-3, etc.'" cover both current and future diseases for which there is no enablement provided. Id. at 3.

Although the Examiner agrees that applicants have provided test assays and procedures related to Aurora-2 kinase, GSK-3, and Src inhibition, the Examiner contends that, "there is nothing in the disclosure regarding how this *in vitro* data

correlates to the treatment of the disorders of the instant claims." Id. Applicants respectfully disagree.

Because claims 14, 20, and 27 recite specific diseases associated with each kinase, they do not cover both current and future diseases for which there is no enablement provided.

Applicants have amended claim 14 to recite specific cancers associated with Aurora-2. Specifically, applicants have amended claim 14 to recite diseases selected from "melanoma, lymphoma, neuroblastoma, leukemia, or a cancer selected from colon, breast, lung, kidney, ovary, pancreatic, renal, CNS, cervical, prostate, or cancer of the gastric tract." The references cited herein link Aurora-2 with the recited cancers. See Bischoff et al., EMBO J., 1998, 17, 3052-3065 (hereafter "Bischoff 1"). See also Bischoff et al., Trends in Cell Biology, 1999, 9, 454-459 (hereafter "Bischoff 2"). Bischoff 1 discloses that Aurora-2 RNA is expressed in a variety of human tumor cell lines while having limited expression in normal human tissue (see page 3060, second column, last paragraph to page 3062, first column, first paragraph). Bischoff 2 is a review article further linking Aurora-2 expression with various human cancers recited in amended claim 14 (see pages 457-458 under the section titled "Aurora2 and Cancer"). Bischoff 1 and Bischoff 2 are enclosed in a Supplemental Information Disclosure Statement filed concurrently herewith.

Applicants have amended claim 20 to recite specific diseases associated with GSK-3 expression. Specifically, applicants have amended claim 20 to recite "diabetes and schizophrenia." The references cited herein link GSK-3 with the recited diseases.

With respect to diabetes, Applicants have submitted herewith, Cline et al., *Diabetes* 51: 2903-2910, 2002 (hereafter "Cline"). Cline discloses that a GSK-3 inhibitor treatment activated glycogen synthase activity in the Zucker diabetic fatty (ZDF) rat model of diabetes, which significantly improved oral glucose disposal and significantly lowered fasting plasma glucose in diabetic rats (see, e.g., page 2909, right column). Similarly, Henriksen et al., *J. Physiol. Endocrinol. Metab.* 284: E892-E900, 2003, (hereafter "Henriksen"), shows that administration of a GSK-3 inhibitor to insulin-resistant diabetic ZDF rats improved whole body glucose disposal and insulin sensitivity (see, e.g., page E899, right column). Taken together with the specification, Cline and Henriksen clearly show that there is a reasonable correlation between the GSK-3 inhibitors of the invention, the *in vitro* data showing their GSK-3 inhibitory activity, and the use of these compounds to treat diabetes. Cline and Henriksen are enclosed in the Supplemental Information Disclosure Statement filed concurrently herewith.

With respect to schizophrenia, applicants have submitted herewith, WO 2004/013140, which describes the use of GSK-3 inhibitors to treat schizophrenia in *in vivo* animal models. WO 2004/013140 discloses mouse models of schizophrenia and anxiety and shows that compounds of the invention had anti-schizophrenic and anxiolytic effects in the respective animal models. See, e.g., Examples 21 and 22 on pages 39-42. WO 2004/013140 is enclosed in the Supplemental Information Disclosure Statement filed concurrently herewith.

Applicants have amended claim 27 to recite specific diseases associated with Src expression. Specifically,

applicants amend claim 27 to recite "hypercalcemia, osteoporosis, osteoarthritis, cancer, symptomatic treatment of bone metastasis, or Paget's disease." The references cited herein link Src with the recited disorders. See Soriano *et al* (Src-deficient mice developed osteopetrosis); Wiener *et al* and Staley *et al* (antisense Src expressed in ovarian and colon tumor cells inhibits tumor growth).

Accordingly, applicants' amendments cover current diseases for which adequate enablement is provided.

The Examiner also contends that, "there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the disorders of the instant claims." Applicants respectfully disagree.

According to the MPEP, "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." Applicants respectfully submit that the specification does describe how this in vitro data correlates to the treatment of disorders through the development and study of kinase-deficient animals, in vitro models, and in vivo models.

The development and study of kinase-deficient animals provide a direct link between the inhibition of a kinase target and the diseases associated with that target. See page 22, lines 12-32.

With respect to Src, for example, Soriano et al found that Src-deficient mice develop osteopetrosis (bone build-up) and thus directly links Src inhibition to the treatment of osteoperosis and other bone-loss disorders. Id. Furthermore, Wiener et al and Staley et al showed that antisense Src

expressed in ovarian and colon tumor cells inhibits tumor growth and thus clearly links the inhibition of Src kinase with the treatment of ovarian and colon cancer. Id.

The development and study of *in* vivo and *in vitro* models also provide direct links between the inhibition of a kinase target and the diseases associated with that target.

With respect to Aurora-2, for example, Harrington, et al, *Nature Medicine* **10**, 262-267 (2004), (hereafter "Harrington, et al"), discuss a potent Aurora kinase inhibitor that caused "profound inhibition of tumor growth in a variety of *in vivo* xenograft models, leading to regression of leukemia, colon and pancreatic tumors at well-tolerated doses." Harrington is enclosed in the Supplemental Information Disclosure Statement filed concurrently herewith.

Additionally, applicants have cite references in the application that detail how Aurora-2 has been found to be over-expressed in human cancer tissue [*see*, Bischoff *et al., EMBO J.*, 1998, 17, 3052-3065; Schumacher *et al. J. Cell. Biol.*, 1998, 143, 1635-1646; and Kimura *et al., J. Biol. Chem.*, 1997, 272, 13766-13771]. These references provide a direct link between Aurora kinase inhibitors and a variety of cancers.

With respect to GSK-3, for example, Henriksen and Cline used rat models to show that administration of a GSK-3 inhibitor to diabetic rats improved glucose disposal. Additionally, applicants have cited references in the application that detail how the inhibition of GSK-3 leads to increased glycogen synthase and glucose uptake. See Klein et al, *PNAS*, **93**, 8455-9 (1996); Cross et al., *Biochem. J.*, **303**, 21-26(1994); Cohen, *Biochem. Soc. Trans.*, **21**, 555-567 (1993); and Massillon et al., *Biochem J.*, **299**, 123-128 (1994).

Additionally, WO 2004/013140 used mouse models to show that GSK-3 inhibitors had anti-schizophrenic and anxiolytic effects. The compounds of WO 2004/013140 inhibit GSK-3 at Ki values similar to that of the compounds of the present invention. Therefore, because of the correlation shown between the *in vitro* and *in vivo* data in WO 2004/013140, one of skill in the art would reasonably expect that the *in vitro* data of the present application would correlate with *in vivo* results as well. Accordingly, these references provide a direct link between GSK-3 kinase inhibitors and diabetes and schizophrenia.

Because the references cited in the present application and the knowledge in the art suggest a correlation between the inhibition of GSK-3, Aurora-2 protein kinase, and Src with the treatment of certain diseases, and because the Examiner has not provided evidence that there is no correlation between the inhibition of GSK-3, Aurora-2 protein kinase, or Src and the treatment of such diseases, applicants respectfully submit that the newly amended claims are indeed enabled.

Accordingly, applicants respectfully request that the Examiner withdraw the rejection of claims 14, 16, 17, 20, 22, and 27.

35 U.S.C. § 103

Claims 1-5 and 9-27 stand rejected under 35 U.S.C. § 103 as being obvious over Bradbury et al., WO 00/39101; Armistead et al., WO/01/60816; or Pease et al., WO 01/64655. Applicants traverse.

The Examiner first contends that the compounds of the instant claims (wherein R^Y is T-R^8 wherein R^8 is halo, C_{1-6}aliphatic, etc.) are positional isomers of the reference

compounds, which are unsubstituted at the analogous position. The Examiner argues that "it would have been obvious to one having ordinary skill in the art at the time of the invention to prepare the instantly claimed compounds because they are positional isomers of the reference compounds." The Examiner contends that a skilled practitioner "would have been motivated to prepare the instantly claimed compounds because such isomeric compounds are suggestive of one another and would be expected to share similar properties." The Examiner cites 3 cases to support his position: (In re Finley, 81 USPQ 383 (CCPA 1949); In re Norris, 84 USPQ 458 (CCPA 1950); and In re Dillon, 16 USPQ2d 1897 (Fed. Cir. 1990)). Applicants traverse.

Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness. According to the MPEP, "to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation ... to modify the reference ... Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations" (MPEP § 2143). For the reasons set forth below, applicants respectfully submit that the Examiner has not established a prima facie case of obviousness.

First, applicants respectfully submit that the Examiner has failed to show that the references teach or suggest all of the claim limitations, as required to support a *prima facie* case of obviousness. Specifically, the references do not teach nor suggest the requirement of substitution at the R^y position, as recited by the claims of the present application. In fact, all three references only claim and disclose compounds

wherein the analogous position to R^Y is H. These references teach away from the idea of substituting at that position.

Second, the Examiner has failed to provide any evidence in the prior art of a suggestion or motivation to modify the reference." The Examiner argues, "isomeric compounds are suggestive of one another and would be expected to share similar properties." According to the MPEP, "[h]omology and isomerism involve close structural similarity which must be considered with all other relevant facts in determining the issue of obviousness. Homology should not be automatically equated with prima facie obviousness because the claimed invention and the prior art must each be viewed 'as a whole.'" MPEP §2144.09. Applicants respectfully submit that the Examiner has automatically equated the positional isomers of the compounds without viewing the application as a whole. As a whole, all three references specifically teach away from the idea of any substitutions at the R^Y position. The Examiner has failed to show any specific suggestion in any of the references to substitute at the R^Y position.

Finally, applicants respectfully submit that the Examiner has not established that there exists the required reasonable expectation of success within the references. According to the MPEP, "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (MPEP 2143.01). Applicants respectfully submit that the cited references provide no reasonable expectation of success and, in fact, teach away from Applicants' claimed invention.

For all of the above reasons, applicants request that the Examiner withdraw these § 103 rejections.

CONCLUSION

Accordingly, applicants request that the Examiner enter the above amendments, consider the foregoing remarks, and allow the pending claims to issue.

If the Examiner believes that a telephone discussion would further issuance of this application, the Examiner is invited to call the undersigned attorney or agent at any time.

Respectfully submitted,

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